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Global Manufacturing 99 :03
Quality Operations

March 18, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane rm. 1061
Rockville, MD 20852

Re: Docket No. 98D-0994
Draft Guidance for Industry on BACPAC I

Dear Sir/Madam:

We appreciate the opportunity to comment on the Draft "Guidance for Industry on BACPAC I: Intermediates in Drug Substance Synthesis; Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Documentation" issued by the Center for Drug Evaluation and Research (CDER), and the Center for Veterinary Medicine (CVM) of the US Food and Drug Administration.

We would like to acknowledge the extensive FDA participation in joint Industry/Agency meetings on the subject of this guidance. We believe that a process of open exchange between industry and regulators is invaluable in developing a document useful to both. Moreover, we concur with the underlying thesis of this guidance that sound scientific data should be used to demonstrate equivalency of material manufactured.

While there is much in this draft guidance document with which we agree, there are still aspects and proposed requirements that cause concern. The most significant aspects with which we disagree are the requirements for Filing Documentation for:

- Site Changes
- Specification ("Other Specification") Changes
- Manufacturing Process Changes

In all of these, this guidance document specifies the data that must be obtained and reviewed and defines the criteria that these data must meet in order to effect these changes. Considering this, it is unnecessary that these data must be reviewed by the Agency prior to implementation. We recommend in all these cases that these changes be filed as part of the Annual Report.

98D-0994

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Following are comments and our recommended improvements for specific sections of the proposed Guidance document:

I. INTRODUCTION

(line 15) The term "raw material" is used, but is not included in the Glossary of Terms

III. ASSESSMENT OF CHANGE

(line 94) This should read "However, other factors (e.g. isomeric ratio) that may be important..."

(line 95) Delete the sentence, "For example, if the drug substance is a mixture of isomers, then the same quantitative mixture should be obtained after the change."

Rationale: the example as stated may easily be misinterpreted and in some cases may be erroneous.

A. Equivalence of Impurity Profiles

(line 120) This should read, "Data to demonstrate adequacy of new analytical methods should be available."

Rationale: Methods validation data is frequently not submitted as part of the filing, particularly relating to in-process test procedures or procedures for testing intermediates, but should be available for review during regulatory inspections.

(line 123-4) This should read "...historic data from up to ten or more premodification batches if possible."

Rationale: There may be times where ten premodification batches have not been produced, particularly for materials produced infrequently. In cases in which there is a large body of data, it should be acceptable to include historical data from more than ten batches.

(line 124) The word "commercial" should be deleted.

Rationale: Developmental, clinical, or validation batches should be allowed to be included as appropriate. It is not the designation of the batches as "commercial" that should determine their inclusion.

(line 132) Delete "at or"

Rationale: This will be consistent with ICH documents

(line 137) Delete "...including residual organic solvents..."

Rationale: The Glossary of Terms adequately defines impurity to include residual solvents without the need for special mention here.

(line 137) Change to read, "Existing impurities are within the established limits or where acceptance criteria do not exist, existing impurities..."

Rationale: Where meaningful specifications have been developed, the comparison should be to these specifications. This would then be comparable to the requirements stated for a drug substance in the next section.

(line 139) Change to read, "Existing impurities are within the established limits or where acceptance criteria do not exist, total impurities..."

Rationale: As above.

(line 149) Delete "...including residual organic solvents..."

Rationale: As above.

B. Equivalence of Physical Properties

(line 191) Change to read, "... unless equivalence of the impurity profile can be demonstrated prior to the API."

Rationale: If equivalence is demonstrated at a crude drug stage, physical properties of the final purified API should not need to be evaluated.

(line 200) Change to read, "Conformance to established acceptance criteria or, where acceptance criteria do not exist, conformance to historical particle size distribution profile."

Rationale: Where meaningful specifications have been developed, the comparison should be to these specifications. This would then be comparable to the requirements stated for morphic form in the previous section.

IV. TYPES OF CHANGE

A. Site, Scale, and Equipment Changes

(line 208) The term "reagent" is used, but is not included in the Glossary of Terms.

1. Site Changes

(line 230) The term should be "operation*al* qualification"

(line 243) Replace "Validation data should be provided for new test methods and also for existing methods if their use is being extended beyond their original purpose." with "These methods should be appropriately validated."

Rationale: This data is not usually included in filings for intermediates.

(line 264) Change to read "...either by the applicant, or by a contract manufacturer..."

Rationale: to eliminate ambiguity that the phase "previously approved...etc" applies only to the contract manufacturer.

(line 266) Change to "Annual Report"

This Guidance Document identifies the data that must be obtained and the criteria that must be met to justify a site change. This should be sufficient, without the need for regulatory review at the time of implementation.

2. Scale Changes

(lines 273-308) This section should be deleted.

Rationale: Unlike dosage form manufacture, scale of manufacture is not routinely specified in regulatory submissions. Scale of a specific batch frequently depends upon the yield of the previous step and all batches in a campaign may be of differing size with ratios (but not absolute quantities) of reactants and solvents specified. If size/scale changes are such that they do not require changes of equipment or parameters, these should not be required to be filed with the Agency.

3. Equipment Changes

(line 316) The term should be "operation*al* qualification"

(line 321-322) Delete examples.

Rationale: The examples are unnecessary. In the reactor example given, the switch from glass to metal may not represent a significant difference.

B Specification Changes

2. Specification Changes That Provide Greater Assurance of Quality

(line 348) Delete "...and validation data"

Rationale: This data is not usually filed for in-process testing or for testing of intermediates.

3. Other Specification Changes

(line 375) Replace "Validation data should be provided for new test methods and also for existing methods if their use is being extended beyond their original purpose." with "These methods should be appropriately validated."

Rationale: This data is not usually included in filings for intermediates.

(line 395) Change to "Annual Report"

This Guidance Document identifies the data that must be obtained and the criteria that must be met to justify the change. This should be sufficient, without the need for regulatory review at the time of implementation.

C Manufacturing Process Changes

1. Changes That Do Not Involve New Starting Materials or Intermediates

(line 417) Replace "Validation data should be provided for new test methods and also for existing methods if their use is being extended beyond their original purpose." with "These methods should be appropriately validated."

Rationale: This data is not usually included in filings for intermediates.

(line 425) Delete "Option 1"

(line 427) Delete "Option 1"

Rationale: Specifying that only one option is acceptable would make this Guidance more stringent than requirements for drug products.

(line 442) Change to "Annual Report"

This Guidance Document identifies the data that must be obtained and the criteria that must be met to justify the change. This should be sufficient, without the need for regulatory review at the time of implementation.

2. Changes in The Route of Synthesis in One or More Steps etc.

(line 456) Replace "Validation data should be provided for new test methods and also for existing methods if their use is being extended beyond their original purpose." with "These methods should be appropriately validated."

Rationale: This data is not usually included in filings for intermediates.

(line 464) Delete "Option 1"

(line 466) Delete "Option 1"

Rationale: Specifying that only one option is acceptable would make this Guidance more stringent than requirements for drug products.

(line 480) Change to "Annual Report"

This Guidance Document identifies the data that must be obtained and the criteria that must be met to justify the change. This should be sufficient, without the need for regulatory review at the time of implementation.

3. Changes in Which an Intermediate Is Redefined as a Starting Material
(line 486) Delete "an increase in"
Rationale: Any change may initiate such a change.
(line 511) Replace "Validation data should be provided for new test methods and also for existing methods if their use is being extended beyond their original purpose." with "These methods should be appropriately validated."
Rationale: This data is not usually included in filings for intermediates.
(line 538) Change to "Annual Report"
This Guidance Document identifies the data that must be obtained and the criteria that must be met to justify the change. This should be sufficient, without the need for regulatory review at the time of implementation.

ATTACHMENT B – GLOSSARY OF TERMS

Batch
(line 571) Change "...drug substance processed in one process..." to "...drug substance produced in one process..."

Drug Substance
(line 576) Add "(also known as Active Pharmaceutical Ingredient)"
Rationale: for consistency with other Guidance documents

Final Intermediate
(line 582) change to read "...covalent bond formation and/or cleavage:..."
Rationale: The final intermediate may be formed in a cleavage reaction.

Final Solution Step
(line 585) Change to read, "The step that includes the solution ..."
Rationale: clarity

Historical Data
(line 589) Change to "...10 or more..."
Rationale: The option should be available to use data from more than 10 batches as the historical baseline.
(line 589) Delete "recent"
Rationale: It is appropriate that the batches be representative of the established process. Specifying the time of manufacture is unnecessary. Moreover, "recent" may be open to differing interpretations.
(line 591) Delete "(The appropriate review division(s)....is based on <10 batches.) and replace with "Justification should be provided for cases in which historical data is based on less than 10 batches."

Isolated Intermediate
(line 607-608) Delete "The isolation or purification procedure should be part of the validated process."
Rationale: This is unnecessary to the definition, and reflects GMPs rather than filing requirements.

Operational Qualification
(line 618) Change "i.e." to "e.g."

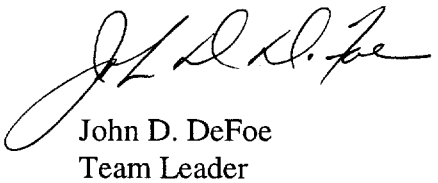
Specification
(lines 631-639) This describes only specifications for drug substances, but should equally apply to specifications for intermediates, starting materials, solvents, or any materials used in production of drug substances.

Starting Material
(line 641) Delete "of an intermediate and/or"
Rationale: The starting material should only relate to the finished drug substance. In many cases, intermediates contain elements such as blocking or protecting groups that are subsequently removed and should not be considered as starting materials.
(line 643) Delete "in the chemical literature"
Rationale: The criteria should be that properties, structure and profile are well defined, not where that information resides.

Total Impurities
(line 644) Change "limit of quantitation" to "threshold of quantitation as defined in ICH Q3A"
Rationale: This is consistent with other Guidances

Pfizer Inc hopes that the foregoing comments will be useful to the FDA in the ongoing development of the Guidance Document for BACPAC I. We appreciate the opportunity to submit comments and thank you for consideration of our recommendations.

Respectfully submitted,



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